

Review Article

Overview of Validation and Basic Concepts of Process Validation

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Abstract: Quality is the primordial intention to any industry and its products manufactured. Multiple views on obtaining such quality are the current interest in the pharmaceutical industry. Validation is the art of designing and practicing the designed steps alongside with the documentation. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. Process Validation emphasize on process design elements and maintaining process control during commercialization and communicate that process validation is an ongoing program and align process validation activities with product lifecycle. Process validation also emphasizes the role of objective measures and statistical tools and analyses and emphasizes knowledge, detection, and control of variability and gives assurance on consistent of quality/productivity throughout life cycle of product.

Keywords: Quality, Validation, Process Validation, Protocol, Prerequisites, Regulatory basis.

INTRODUCTION

The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever increasing interest in validation owing to their industry's greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation [1].

Validation is a concept that has evolved in United States in 1978. The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labeling or process control. Validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP [2].

The word validation simply means assessment of validity or action of proving effectiveness. Validation is a team effort where it involves people from various disciplines of the plant.

This principle incorporates the understanding that the following conditions exist: Quality, safety, and efficacy are designed or built into the product. Quality cannot be adequately assured merely by in-process and finished product inspection or testing each step of a manufacturing process is controlled to assure that the

finished product meets all quality attributes including specifications.

The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. Process controls include raw materials inspection, in-process controls and targets for final product. The purpose is to monitor the online and off-line performance of the manufacturing process and then validate it. Even after the manufacturing process is validated, current good manufacturing practice also requires that a well-written procedure for process controls is established to monitor its performance [3].

Validation mainly based on, FDA regulations describing current good manufacturing practice (cGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211. The cGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is required, in both general and specific terms, by the cGMP regulations in parts 210 and 211 [4].

HISTORY OF VALIDATION

The concept of validation was first proposed by two FDA officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals (Agalloco 1995). It was proposed in direct response to several problems in the sterility of

large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated process of pharmaceutical.

U.S.F.D.A. was the pioneer in advocating the concept of process validation, but till 29th September 1978 the definition of process validation did not appear in any part of literature of U.S.F.D.A. no cGMP regulations talked anything about process validation [5].

Definitions [6-8]

European commission

1991 –Validation-“Act of proving, in accordance of GMPs that Any...” process actually leads to expected results.

2000 -“Documented evidence that the process, operated within established Parameters, can perform effectively and reproducibly to produce a Medicinal product meeting its predetermined specifications and quality attributes”.

US FDA Definition

“Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics.”

ICH Definition

“Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality.”

WHO Definition

“The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to expected result.”

Need of Pharmaceutical Validation [9]

Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.

Assurance of Quality

Without validation, a process that is well understood and in a state of confidence, control of quality of the

product manufactured cannot be assured without validation

Cost Reduction

Since each and every step in validation is monitored constantly there lesser rejects and reworks which would lead to an effective cost reduction.

Government Regulation

Validation is considered to be an integral part of GMPs. Worldwide compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products.

The FDAs cGMP refer to the concepts of the validation in 211.110 and 211.113 sections. Section 211.110 states that, such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in process materials and drug product.

The accuracy, sensitivity, specificity and reproducibility of test methods employed by the firm shall be established and documented.

A general requirement for process validation is contained in the medical device cGMP, regulation, section 820.100(b) (1) which states that, “Where deviations from device specifications could occur as a result of the manufacturing process itself, there shall be written procedures describing any processing controls necessary to assure conformance to specifications.”

Scope of Validation

Pharmaceutical Validation is a vast area of work and it practically covers every aspect of pharmaceutical processing activities, hence defining the Scope of Validation becomes a really difficult task. However, a systematic look at the pharmaceutical operations will point out at least the following areas for pharmaceutical validation; [10]

- Analytical
- Instrument Calibration
- Process Utility services
- Raw materials
- Packaging materials
- Equipment
- Facilities
- Manufacturing operations
- Product Design
- Cleaning
- Operators

Importance of Validation [11, 12]

- Assurance of quality
- Time bound
- Process optimization

- Reduction of quality cost
- Nominal mix-ups, and bottle necks
- Minimal batch failures, improved efficiency and productivity
- Reduction in rejections
- Increased output
- Avoidance of capital expenditures
- Fewer complaints about process related failures
- Reduced testing in process and in finished goods
- More rapid and reliable start-up of new equipments
- Easier scale-up form development work
- Easier maintenance of equipment
- Improved employee awareness of processes
- More rapid automation
- Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products)

Planning for Validation: [13]

All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

- The VMP should be a summary document, which is brief, concise and clear.
- The VMP should contain data on at least the following:
 - Validation policy.
 - Organizational structure of validation activities.

- Summary of facilities, systems, equipment and processes to be validated.
- Documentation format: The format to be used for protocols and reports.
- Planning and scheduling.
- Change control.
- Reference to existing document.
- In case of large projects, it may be necessary to create separate validation master plans.

Validation Set Up [14]

To establish the desired attributes. These attributes include physical as well as chemical characteristics. In the case of parenterals, these desirable attributes should include stability, absence of pyrogens, and freedom from visible particles.

Acceptance specifications for the product should be established in order to attain uniformity and consistently the desired product attributes, and the specifications should be derived from testing and challenge of the system on sound statistical basis during the initial development and production phases and continuing through subsequent routine production.

The process and equipment should be selected to achieve the product specification. For example; design engineers; production and quality assurance people may all be involved. The process should be defined with a great deal of specificity and each step of the process should be challenged to determine its adequacy. These aspects are important in order to assure products of uniform quality, purity and performance.

Table 1: Validation Team and Responsibilities [15]

| Department | Designation | Responsibility |
|--------------------------------|-----------------------------------|---|
| Research and development (R&D) | Executive/Officer | To coordinate the entire validation process by scheduling meetings and discussions with production, quality control and quality assurance. Preparation of preliminary validation protocol, master formula record, monitoring the process, compiling and analyzing data and test results and preparing the final report. To review the preliminary validation documents. |
| Quality assurance | Officer | To coordinate the entire validation process by scheduling meetings and discussions with the team. Preparation of validation protocol, monitoring the process, compiling and analyzing data and test results and preparing the final report. To review of validation documents. |
| Production | Officer | To participate in performing the validation steps during manufacturing processes. To assist in collection of data. |
| Quality control | Officer | To test and report the test results |
| Quality assurance | General manager Quality assurance | To approve the process validation protocol and report. To review of validation documents. To approve the process. |

Four Major Advantages of Validation Namely [9, 16]

Assurance of Quality

Validation is an extension of the concepts of quality assurance since close control of the process is necessary to assure product quality and it is not possible to control a process properly without thorough knowledge of the

capabilities of that process without validated and controlled processes, it is impossible to produce quality products consistently. End product testing, in the absence of validation, gives little assurance of quality for variety reasons, among which are

- Very limited sample size.
- The limited number of tests performed on a sample. For example, it is impractical to test for all potential impurities or contaminants.
- The limited sensitivity of the test

Process Optimization

The optimization of a process for maximum efficiency, while maintaining quality standards, is a consequence of validation. Literal meaning of word to optimize is “To make as effective, perfect or useful as possible”. The optimization of the facility, equipment, systems, and processes results in a product that meets quality requirements at the lowest cost.

Reduction of Quality Costs

Quality costs are divided in to four categories. They are:

- Preventive costs.
- Appraisal costs.
- Internal failure costs.
- External failure costs.

e.g.: of internal failure costs: Any validated and controlled process will result in fewer internal failures like

- Fewer rejects
- Reworks
- Re-tests
- Re-inspection

Process validation makes it possible to do the job right the first time. Also, a scientifically studied and controlled process makes it unlikely that defective products will be dispatched to market thus no recalls or market complaints.

Safety

Validation can also result in increased operation safety. e.g.: gauges used on equipment that designed to operate at certain temperature and pressures must be reliable i.e. they must be calibrated.

TYPES/METHODS OF VALIDATION [17, 18]

Prospective Validation

It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol. This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process. Performed on at least three successive production-sizes (Consecutive batches).

In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase, the production process should be categorized into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiment should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol.

All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.

Using this defined process a series of batches should be produced. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process.

In practice, it may take some considerable time to accumulate these data. Some considerations should be exercised when selecting the process validation strategy. Amongst these should be the use of different lots of active raw materials and major excipients, batches produced on different shifts, the use of different equipment and facilities dedicated for commercial production, operating range of the critical processes, and a thorough analysis of the process data in case of Requalification and Revalidation.

During the processing of the validation batches, extensive sampling and testing should be performed on the product at various stages, and should be documented comprehensively. Detailed testing should also be done on the final product in its package.

Upon completion of the review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production. These should be incorporated into the Batch manufacturing and packaging record or into appropriate standard operating procedures.

Limits, frequencies and action to be taken in the event of the limits being exceeded should be specified.

Prospective validation should include, but not be limited to the following:

- Short description of the process.

- Summary of the critical processing steps to be investigated.
- List of the equipment/facilities to be used (including measuring, monitoring/recording equipment) together with its calibration status.
- Finished product specifications for release.
- List of analytical methods, as appropriate.
- Proposed in-process controls with acceptance criteria.
- Additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate.
- Sampling plan.
- Methods for recording and evaluating results.
- Functions and responsibilities.
- Proposed timetable.

Batches made for process validation should be the same size as the intended Industrial scale batches. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise and the marketing authorization.

Concurrent Validation

It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation.

- This validation involves in-process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.
- In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
- The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.
- Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective Validation

It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information. This is achieved by the review of the historical manufacturing testing

data to prove that the process has always remained in control. This type of validation of a process for a product already in distribution.

Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance logbooks, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet the specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.

For retrospective validation, generally data from ten to thirty consecutive batches should be examined to access process consistency, but fewer batches may be examined if justified.

Some of the essential elements for Retrospective Validation

Batches manufactured for a defined period (minimum of 10 last consecutive batches). Number of lots released per year.

- Batch size/strength/manufacturer/year/period.
- Master manufacturing/packaging documents.
- Current specifications for active materials/finished products.
- List of process deviations, corrective actions and changes to manufacturing documents.
- Data for stability testing for several batches.

Revalidation

Re-validation provides the evidence that changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process.

Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

Revalidation becomes necessary in certain situations. Some of the changes that require validation are as follows:

- Changes in raw materials (physical properties such as density, viscosity, particle size distribution and moisture etc that may affect the process or product).
- Changes in the source of active raw material manufacturer.
- Changes in packaging material (primary container/closure system)
- Changes in the process (e.g., mixing time, drying temperatures and batch size)
- Changes in the equipment (e.g., addition of automatic detection system). Changes of equipment which involve the replacement of equipment on a “like for like” basis would not normally require re-validation except that this new equipment must be qualified.
- Changes in the plant/facility.

A decision not to perform revalidation studies must be fully justified and documented.

Basic Concept of Process Validation

Pharmaceutical Process Validation is the most important and recognized parameters of cGMPs. The requirement of process validation appears of the quality system (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use [19].

Process validation is a key element in assuring that these principles and goal are met. The process validation is standardization of the validation documents that must be submitted with the submission file for marketing authorization. The process validation is intended to assist manufacturers in understanding quality management system (QMS) requirements concerning process validation and has general applicability to manufacturing process. According to FDA,

Assurance of product quality is derived from careful and systemic attention to a number of importance factors, including: selection of quality process through in-process and end product testing [20].

The basic principle for validation may be stated as follows: [21, 22]

Installation Qualification (IQ)

Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendation of the supplier of the equipment are suitably considered.

IQ considerations are:

- Equipment design features (i.e. material of construction clean ability, etc.)
- Installation conditions (wiring, utility, functionality, etc.)
- Calibration, preventative maintenance, cleaning schedules.
- Safety features.
- Supplier documentation, prints, drawings and manuals.
- Software documented.
- Spare parts list.
- Environmental conditions (such as clean room requirements, temperature, and humidity).

Operational Qualification (OQ)

Establishing by objective evidence process control limits and action levels which result in product that all predetermined requirements.

OQ considerations include:

- Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
- Software parameters.
- Raw material specifications
- Process operating procedures.
- Material handling requirements.
- Process change control.
- Training.
- Short term stability and capability of the process, (latitude studies or control charts).
- Potential failure modes, action levels and worst-case conditions.
- The use of statistically valid techniques such as screening experiments to optimize the process can be used during this phase.

Performance Qualification (PQ)

Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

PQ considerations include:

- Actual product and process parameters and procedures established in OQ.
- Acceptability of the product.
- Assurance of process capability as established in OQ.
- Process repeatability, long term process stability.

Re – Qualification

Modification to, or relocation of equipment should follow satisfactory review and authorization of the documented change proposal through the change control procedure. This formal review should include consideration of re qualification of the equipment. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system of the preventive maintenance program.

The Regulatory Basis for Process Validation [23, 40]

The concept of process validation from its beginnings in the early 1970s through the regulatory aspects associated with current good manufacturing practice (cGMP) regulations and the application thereof to various analytical, quality assurance, pilot plant, production, and sterile product and solid dosage forms considerations. In the early 1990s, the concept of preapproval inspection (PAI) was born and had as one of its basic tenets the assurance that approved validation protocols and schedules were being generated and that comprehensive development, scale-up, and bio batch and commercial batch validation data were required in order to achieve a successful regulatory PAI audit.

There are several important reasons for validating a product and/or process. First, manufacturers are required by law to conform to cGMP regulations. Second, good business dictates that a manufacturer avoids the possibility of rejected or recalled batches. Third, validation helps to ensure product uniformity, reproducibility, and quality. Although the original focus of validation was directed towards prescription drugs, the FDA Modernization Act of 1997 expanded the agency's authority to inspect establishments manufacturing over-the-counter (OTC) drugs to ensure compliance with cGMP.

Once the concept of being able to predict process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis for requiring process validation. The cGMP regulations for finished pharmaceuticals, 21 CFR 210 and 211, were promulgated to enforce the requirements of the act. FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The cGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance

of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)).

Once the concept of being able to predict process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis for requiring process validation. The ultimate legal authority is Section 501(a) (2) (B) of the FD&C Act, which states that a drug is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or were not operated or administrated in conformity with cGMP. Assurance must be given that the drug would meet the requirements of the act as to safety and would have the identity and strength and meet the quality and purity characteristics that it purported or was represented to possess. That section of the act sets the premise for process validation requirements for both finished pharmaceuticals and active pharmaceutical ingredients, because active pharmaceutical ingredients are also deemed to be drugs under the act. The cGMP regulations for finished pharmaceuticals, 21 CFR 210 and 211, were promulgated to enforce the requirements of the act. Although these regulations do not include a definition for process validation, the requirement is implicit in the language of 21 CFR 211.100, which states: "There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess."

Prerequisite of Process Validation [24]

- Process Development Designee shall review the product development report, data from pilot scale, scale up batch and proposed master formula document of product intended for manufacturing.
- Process Development Designee shall review/ensure the availability analytical method transfer report to the plant and plant preparedness for conducting validation testing and routine testing; function shall co-ordinate with QC/QA in this regards [25].
- Process Development Designee shall prepare commercial/exhibit batch production and control records which include the operational limits and overall strategy for process control based on development report.
- The Process Validation is performed after the facility, utility, and equipment, and laboratory test methods have been validated and released for process validation activities. Where compendia method is used only limited analytical method validation shall be conducted.
- All raw material and packaging material specification shall be from approved vendors and shall be approved by quality control.

- All the equipment and instrument to be utilized are calibrated and preventive maintenance programs are in place.
- Relevant SOPs are in place and training is completed on equipment, operation, manufacturing instruction and sampling strategy.
- Key process steps and process variables are identified and their operating ranges have been established.
- All the master formula, manufacturing instruction, packaging instruction, testing procedure and specification shall be approved before execution of process validation batches.
- The cleaning of the area and equipment has been completed prior to the initiation of process validation.
- The validation team and operational team shall be trained from process engineer [27].

Strategy for Industrial Process Validation of Solid Dosage Forms [26]

The strategy selected for process validation should be simple and straightforward. The following five points gives strategy for process validation.

- The use of different lots of raw materials should be included. i.e., active drug substance and major excipients.
- Batches should be run in succession and on different days and shifts (the latter condition, if appropriate).
- Batches should be manufactured in the equipment and facilities designated for eventual commercial production.
- Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications.
- Failure to meet the requirements of the Validation protocol with respect to process input and output control should be subjected to process requalification and subsequent revalidation.

Process Validation within the Quality Management System [27]

Process validation is part of the integrated requirements of a quality management system. It is conducted in the context of a system including design and development control, quality assurance, process control, and corrective and preventive action. The product should be design robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Corrective actions often identify inadequate processes/process validations. Each corrective action applied to a manufacturing process should include the

consideration for conducting process validation/revalidation.

Reason for Process Validation [28]

The possible reason of performing process validation may include:

- New product or existing products as per SUPAC changes.
- Change in site of manufacturing.
- Change in batch size.
- Change in equipment.
- Change in process existing products.
- Change in composition or components.
- Change in the critical control parameters.
- Change in vendor of API or critical excipient.
- Change in specification on input material.
- Abnormal trends in quality parameters of product through review during Annual Product Review (APR).
- Trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.

Benefits of Process Validation [27]

- Consistent through output.
- Reduction in rejections and reworks.
- Reduction in utility cost.
- Avoidance of capital expenditures.
- Fewer complaints about process related failure.
- Reduced testing in process and finished goods.
- More rapid and accurate investigations into process deviation.
- More rapid and reliable start-up of new equipment.
- Easier scale-up from development work.
- Easier maintenance of equipment.
- Improve employee awareness of processes.
- More rapid automation.

Stages of Process Validation [29, 30]

Process Validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process Validation involves a series of activities taking place over the lifecycle of the product and process. The activities relating to validation studies may be classified into three stages:

Stage 1 – Process Design

“Focusing exclusively on qualification efforts without also understanding the manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. It covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production documents, operational qualification, process capability. Also this is the stage in which the establishment of a strategy for process control is taking place using accumulation knowledge and understanding of the process.”

Stage 2 – Process Qualification

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. It confirms that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under “worst case” conditions. GMP compliant procedures must be followed in this stage and successful completion of this stage is necessary before commercial distribution of a product.

There are two aspect of Process Qualification:

- Design of Facilities and Qualification of Equipment and Utilities
 - Proper design of manufacturing facility is desired under 21 CFR part 211, subpart C, of the cGMP regulation on Buildings and Facilities.
 - Activities performed to assure proper facility design and that the equipment and utilities are suitable for their intended use and perform properly.
- Process Performance Qualification
 - “Criteria and process performance indicators that allow for a science and risk-based decision about the ability of the process to consistently produce quality products”.
 - Part of the planning for stage 2 involves defining performance criteria and deciding what data to collect when, how much data, and appropriate analysis of the data.
 - Likely consist of planned comparisons and evaluations of some combination of process measures as well as in-process and trial product attributes.
 - Manufacturer must scientifically determine suitable criteria and justify it.
 - Objective measures, where possible.
 - May be possible to leverage earlier study data if relevant to the commercial scale.

Stage 3 – Continued Process Verification

Ongoing assurance is gained during routine production that the process remains in a state of control. The validation maintenance stage requires frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures.

A successful validation program depends on the knowledge and understanding and the approach to control manufacturing processes. These include the source of variation, the limitation of the detection of the variation, and the attributes susceptible of the variation.

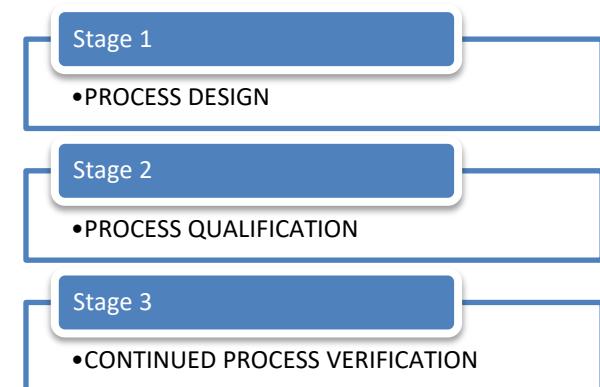


Fig. 1: Approaches to Process Validation

Primary Packing Validation Approach

Primary packing will be done for individual packing ,the process validation protocol shall be clearly state the variable(s) which impact the integrity of the primary pack and set parameters range, primary packing is mostly change part specific and it is mandatory for all new products .

For existing products it shall be performed based on matrix approach w.r.t pocket size for blister /strip and different size of HDPE bottles/containers.

The activity starts with documenting the change part number and establishing the proven acceptance range-PAR for the machine set parameters

e.g.: Sealing temp/speed in blister and strip packing machine, for dry syrups /sterile products speed and sealing torque, for tablets capsules bulk packed in HDPE bottles ,the speed and induction sealing ,power voltage and conveyer speed for topically filled in collapsible tubes ,speed and crimping quality PAR shall be established for each configuration.

Phases in Process Validation [31, 32]

The activities relating to validation studies may be classified into three:

Phase1: Pre-Validation Qualification Phase

This phase is covers all activities relating to product research and development, formulation pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions and storage, and handling of in-process and finished dosage forms, equipment qualification, installation qualification master production document, operational qualification and process capacity.

Phase 2: Process Validation Phase

It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory products can be produced even under the worst conditions.

Phase 3: Validation Maintenance Phase

Phase 3: Validation/Maintenance Phase

It requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations, failures and modifications to the production process and that all standard operating procedures (SOPs), including change control procedures, have been followed. At this stage, the validation team comprising of individuals representing all major departments also assures that there have been no changes/deviations that should have resulted in requalification and revalidation. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications. It is assumed that throughout manufacturing and control, operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture.

- Objectives, scope of coverage of the validation study.
 - Validation team membership, their qualifications and responsibilities.
 - Type of validation: prospective, concurrent, retrospective, re-validation.
 - Number and selection of batches to be on the validation study.
 - A list of all equipment to be used; their normal and worst case operating parameters.
 - Outcome of IQ, OQ for critical equipment.
 - Requirements for calibration of all measuring devices.
 - Critical process parameters and their respective tolerances.
 - Process variables and attributes with probable risk and prevention shall be captured.
 - Description of the processing steps: copy of the master documents for the product.
 - Sampling points, stages of sampling, methods of sampling, sampling plans.
 - Statistical tools to be used in the analysis of data.
 - Training requirements for the processing operators.
 - Validated test methods to be used in in process testing and for the finished product.
 - Specifications for raw and packaging materials and test methods.
 - Forms and charts to be used for documenting results.
 - Format for presentation of results, documenting conclusions and for approval of study results.

Validation Master Plan [34]

The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of it being the list/inventory of the items to be validated and the planning schedule.

All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan.

It should comprise all prospective, concurrent and retrospective validations as well as revalidation.

The Validation Master Plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents,

SOP's and validation protocols and reports. The format and content should include:

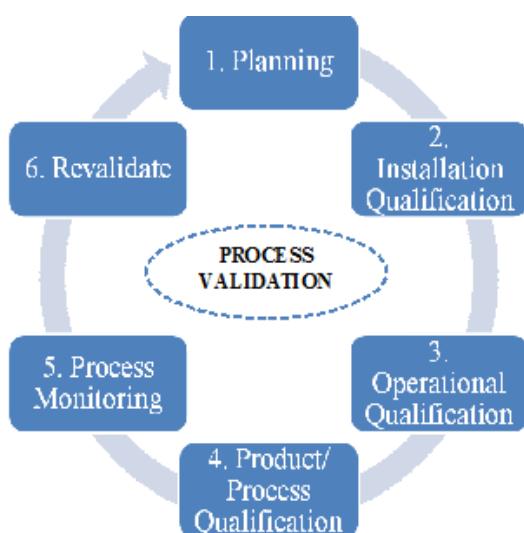


Fig. 2: Phases in Process Validation

Validation Protocol [33]

Detailed protocols for performing validations are essential to ensure that the process is adequately validated. Process validation protocols should include the following elements:

- Introduction: validation policy, scope, location and schedule.
- Organizational structure: personnel responsibilities.
- Plant/process/product description: rational for inclusions or exclusions and extent of validation.
- Specific process considerations that are critical and those requiring extra attention.
- List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach.
- Re-validation activities, actual status and
- Key acceptance criteria.
- Documentation format.
- Reference to the required SOP's.
- Time plans of each validation project and sub-project.

Process Validation and Quality Assurance [35]

The relationship of quality assurance and process validation goes well beyond the responsibility of any quality assurance (QA) function. Nevertheless, it is a fair to say that process validation is a QA tool, because it establishes a quality standard for the specific process.

Quality assurance in pharmaceutical companies embodies the effort to assure that products have the strength, purity, safety and efficacy represented in the company's new drug application (NDA) filings.

Although quality assurance is usually designated as a departmental function, it must also be an integral part of an organization's activities. When process validation becomes a general objective of the technical and operational groups within an organization, it becomes the driving force for quality standards in development work, engineering activities, quality assurance, and production.

The quality assurance associated with the pharmaceutical development effort includes the following general functions:

- To ensure that a valid formulation is designated.
- To qualify the process that will be scaled up to production-size batches.
- To assist the design of the validation protocol.
- To manufacture the bio batches for the clinical program, which will become the object of the FDA's preapproval clearance.

To work with production and engineering to develop and carry out the qualification program for production equipment and facilities/process systems.

To develop validated analytical methods to allow:

- The stability program to be carried out.
- The testing of raw materials and finished product
- The development of release specifications for the raw materials and finished product.
- The testing of processed material at certain specified stages.

Quality assurance is the effort taken to ensure compliance with government regulations for the systems, facilities, and personnel involved with manufacturing products. QA audits will be quite varied in scope to achieve this assurance. These responsibilities include batch record reviews, critiques of product design, process validation activity, and, possibly, audits of other departments operations.

Validation Report [36, 37]

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated). The report should include at least the following:

- Title and objective of study.
- Reference to protocol.
- Details of material.
- Equipment.
- Programmes and cycles used.
- Details of procedures and test methods.
- Results (compared with acceptance criteria).
- Recommendations on the limit and criteria to be applied on future basis.

Documentation [38, 39]

A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.

A report that cross-references the qualification and/or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.

After completion of a satisfactory qualification, a format release for the next step in qualification and validation should be made as a written authorization.

The degree and type of documentation required by cGMP is greatest during process qualification, and continued process verification. Studies during these stages must conform to cGMPs and must be approved by the quality unit in accordance with the regulations (21 CFR 211.22 and 211.100).

CONCLUSION

Validation is the most widely used word in the areas of drug development, manufacturing and specification of finished products. The consistency and reliability of a validated process to produce a quality product is the very important for an industry. Pharmaceutical Process Validation is the most important and recognized parameters of cGMP. The process validation is intended to assist manufacturers in understanding quality management system (QMS) requirements concerning process validation and has general applicability to manufacturing process.

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